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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/787,097	06/27/2001	Jonathan S. Duke-Cohan	00530-089002	1296

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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 03/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/787,097	DUKE-COHAN ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *17 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-46* is/are pending in the application.

4a) Of the above claim(s) *4,5,7-19 and 28-37* is/are withdrawn from consideration.

5)☐ Claim(s) *2,3 and 38-40* is/are allowed.

6)☒ Claim(s) *1, 6, 20-27, and 41-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment, filed 5/5/03, is acknowledged.

2. Claims 1-46 are pending.

3. Claims 4-5, 7-19, and 28-37 stand withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention.

4. Claims 1-3, 6, 20-27, and 38-46 are under consideration in the instant application.

5. The finality of the pervious rejection is hereby withdrawn, a new ground of rejection is set forth herein.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1, 6, 20-27, and 41-46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the isolated DNA sequence of SEQ ID NOs: 1, 11, 13 and 19 for detection assay; does not reasonably provide enablement for an isolated DNA comprising (a) a nucleic acid sequence that (i) encodes a polypeptide that enhances spreading of a macrophage or a monocyte and (ii) hybridizes to the complement of SEQ ID NO: 13 under the specific conditions recited in claim 1 (b) the complement of the nucleic acid sequence in claim 1, an isolated nucleic acid comprising a sequence encoding a fusion protein comprising a first domain and a second domai, wherein the amino acid sequence of the first domain comprises SEQ ID NO: 12 or a functional fragment thereof and wherein the second domain comprises a heterologous sequence in claim 6, an isolated DNA comprising (a) a nucleic acid sequence that is at least 85%, 95% identical to SEQ ID NO: 13; or the complement of the nucleic acid sequence, wherein the nucleic acid sequence encodes a polypeptide that enhances spreading of a macrophage or a monocyte in claims 41and 42 or any isolated DNA comprising (a) nucleic acid sequence that encodes a polypeptide consisting of an amino acid sequence that is at least 85%, 95% or 98% identical to SEQ ID NO:12, or the complement of the nucleic acid sequence, wherein the polypeptide enhances spreading of a macrophage or a monocyte. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for the same reasons set forth in the previous Office Action mailed 7/15/03.

Further, the fact that two nucleic acid sequences will hybridize under moderate or stringent conditions does not in and of itself require that the two sequences share any functional activity. Thus the same observations apply to the recitation of a nucleic acid that "hybridizes to the

complement of SEQ ID NO: 13". Further, it was well known in the art at the time the invention was made that hybridization could occur between two sequence based upon short stretches of 100% identity. Thus a great deal of sequence variability *with respect to the full-length nucleic acid* is possible. In the absence of a clear recitation that the identity is over the full length of SEQ ID NO:13 the claim reads on subsequences. It would require undue experimentation of the skilled artisan to determine which subsequences of SEQ ID NO:13 would hybridize to the complement of SEQ ID NO: 13, and in turn identify whether the nucleic acid sequence encodes a polypeptide that have the function of the full length molecule (i.e., enhances spreading of a macrophage or a monocyte). Thus as for the recitation of hybridization language in the absence of the *sequence length over which the hybridization takes place*; does not allow the skilled artisan to make and use the hybridizing nucleic acids commensurate in scope with the instant claims without undue experimentation.

The state of the prior art as exemplified by Sambrook et al, newly cited, is such that determining the specificity of hybridization probes is empirical by nature and the effect of mismatches within oligonucleotide probes is unpredictable. Furthermore, there is no limitation on the size of the claimed polynucleotide or that the claimed polynucleotide be completely complementary to the SEQ ID NO:13-derived probe. Since Claim 1 encompasses any nucleic acid in length that hybridizes to the complement of SEQ ID NO:13, the predictability of which oligonucleotides or probes hybridize specifically to said polynucleotide encoding a polypeptide that enhances spreading of a macrophage or a monocyte would require undue experimentation of one skilled in the art to practice the claimed invention.

Applicant's arguments, filed 2/17/04, have been fully considered, but have not been found convincing.

Applicant argues that there is no "bright line" rule establishing the number of members of a genus disclosed in a specification that is required in order to establish enablement of the genus. Applicant submits that one of skill in the art would know, from the teaching of the specification in regard to making (e.g., at page 24, line 14, to page 26, line 21, page 39, line 5, to page 40, line 8; and page 49, line 5, to page 51, line 2) and using (e.g., at page 26, line 23, to page 34, line 32, and Examples 2, 5, 6, and 10) the three proteins having SEQ ID NOs:2, 10 and 18, and from the art, how to make and use the genus of functional fragments specified by claim 6.

However, the term "comprising" is an open-ended and expand the amino acid fragments of SEQ ID NO: 12 to include additional non disclosed amino acids on either or both sides of the N-terminal or C-terminal of the fragments. Further, the specification fails to provide sufficient guidance as to which core structure of SEQ ID NO: 12 is essential for maintain its enhancement of spreading of a macrophage or a monocyte activity and which changes can be made in the structure of SEQ ID NO: 12 and still maintained the same function.

Applicant argues that the examiner has not explained why the guidance in the specification is not reasonable, nor why any needed experimentation would not be routine.

Again, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the fragments, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Due to the large quantity of experimentation necessary to obtain "fragments" of SEQ ID NO: 12 and attractin-2, to generate the infinite number of derivatives recited in the claims (for at least 85%, 5%, 2% of SEQ ID NO:12, and to determine the specific activity of the infinite fragments/variants, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, the state of the prior art which establishes that biological activity cannot be predicted based on structural similarity, and the breadth of the claims which embrace a broad class of structural variants, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Applicant contends that the recitation of Skolnick et al, Attwood that assigning functional activities based on sequence homology is unpredictable is not relevant to the present situation. Applicant submits that the cited articles address the problem of guessing the biological activity of proteins encoded by newly discovered genes where nothing is known about the gene except that it shares some degree of homology with previously studied gene. Applicant submits that one of ordinary skill in the art need not resort to comparing all random genes in any given genome to SEQ ID NO:13 and guessing that if some homology is shared with SEQ IDNO: 13, it might encode a protein with the desired activity. Applicant submits that in instant case if one of ordinary skill wished to find variants with 85%, 95% or 98% identity to SEQ ID NO: 13 or 12, it is a simple matter to change one or two or more codons and test the encoded polypeptide.

Applicant is relying upon certain biological activities and the disclosure of three species to support an entire genus. The claims as written encompass a broad genus of nucleic acids/polypeptides with an unlimited number of possibilities with regard to the length of the nucleic acid/polypeptide sequence. Further, the enablement issues of making the nucleic acid encoding the protein still remain because the specification does not teach and provide sufficient guidance as to which functional fragment of SEQ ID NO:12 would lead to enhancement of spreading of a macrophage or a monocyte. In addition, the enablement issues of making the nucleic acid still remain because the specification does not teach and provide sufficient guidance as to which nucleic acid of SEQ ID NO:13 would have been altered such that the resultant nucleic acid sequence would have retained the function of enhancing the spreading of macrophage or a monocyte. In addition, variation up to 15% of SEQ ID NO: 13 (643×4^{15}), 5% of SEQ ID NO: 13 (214×4^{5}), 15% of SEQ ID NO:12 (214×19^{15}), 5% of SEQ ID NO:12 (71×19^{5}) and 2% of SEQ ID NO:12 (28×19^{2}) provide a range of activities, not all which are necessarily predictive of enhances spreading of a macrophage or a monocyte. Therefore, absent the ability to predict which of these nucleic acid/polypeptides would function as claimed, and given the lack of data on regions critical for activity, for one of skill in the art to practice the invention as claimed would require a level of experimentation that is excessive and undue.

Applicant submits that the specification disclosed how to make and use three species that fall within the scope of claims 41 and 43. These three sequences are SEQ ID NO:13 itself and two variants of SEQ ID NO:13 (i.e., SEQ ID NO:1 1 and SEQ ID NO:19) that lack either the transmembrane domain-encoding segment of SEQ ID NO:13 or a segment of 222 nucleotides in the 5' region of SEQ ID NO:13 (see, e.g., Examples 8 and 9). Applicant concluded that the specification discloses splice variant cDNAs with SEQ ID NOs: 1, 11, and 19 (encoding proteins with SEQ ID NOs: 2, 10, and 18, respectively). Applicant submits the specification indicates that SEQ ID NO:11 is 94.9%, SEQ ID NO:19 is 88.6%, and SEQ ID NO: 1 is 83.5% identical to SEQ ID NO: 13. Applicant submits that the splice variants with SEQ ID NOs: 11, 13, and 19 fall within the range of levels of identity ("at least 85%") specified by claim 41. The variant with SEQ ID NO:13 falls within the higher range of levels of identity ("at least 95%") specified by claim 42 while that with SEQ ID NO:1 1 is only 0.1% outside of this range.
Applicants submit that from the teaching by the specification of how to make and use the DNAS with SEQ ID NOs: 11, 13, and 19, and the art, one of skill in the art would know, without undue experimentation, how to make and use species falling with scope of claims 41 and 42.

Contrary to applicant assertion SEQ ID NO: 11, 13 and 19 are only splice variant of SEQ ID NO: 13. No addition, substitution of the nucleic acid of SEQ ID NO: 13 or the encoded polypeptide of SEQ ID NO: 12 has been show to have the same function as the full length of the attraction-2 full length polypeptide encoded by SEQ ID NO:13.

7. Claims 6, 24-27 and 46 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the same reasons set forth in the previous Office Action mailed 7/15/03.

Applicant is in possession of an isolated DNA sequence of SEQ ID NOs: 1, 11, 13 and 19 for detection assay.

Applicant is not in possession of an isolated nucleic acid comprising a sequence encoding a fusion protein comprising a first domain and a second domain, wherein the amino acid sequence of the first domain comprises SEQ ID NO: 12 or any "functional fragment" thereof and wherein the second domain comprises a heterologous sequence in claim 6.

Applicant's arguments, filed 2/17/04, have been fully considered, but have not been found convincing.

Applicant submits that considerable disclosure of functional fragments is provided in the specification such as the three proteins (i.e., those with SEQ ID NOs: 2, 10, and 18) disclosed in the present specification were not strictly fragments of the protein with SEQ ID NO:12, they are informative with respect to such fragments. Applicant submits that the structure of every "functional fragment" of claim 6 must be a subset of SEQ ID NO:12, and thus is rigidly

circumscribed; in contrast, the specification in Lilly provided no clue to the structures of the molecules encompassed by the claimed genus of cDNAs, other than the rat cDNA sequence. Applicant submits that one of ordinary skill, reading the specification, could picture immediately a multitude of other species that would be expected to be "functional fragments" of SEQ ID NO:12, simply by virtue of containing most of SEQ I.D NO: 1 2. Applicants submit that one of skill in the art would understand from the teaching of the specification that the inventors were in possession of the invention specified by claims 6, 24-27, and 46.

Contrary to Applicants' assertions, the specification fails to provide sufficient guidance as to which core structure of SEQ ID NO: 12 encoded by the claimed SEQ ID NO: 13 is essential to maintain its functional activity and which changes can be made in the structure of encoded SEQ ID NO: 12 and still maintained the same function.

There is no described or art-recognized correlation or relationship between the structure of the invention, attractin-2 and it's enhancement of spreading of a macrophage, the feature deemed essential to the instant invention. Therefore, one of skill in the art would not envisage, based on the instant disclosure, the claimed genus of fragments of SEQ ID NO:12 which retain the features essential to the instant invention..

8. Claim 2-3 and 38-40 are allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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March 4, 2004

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